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Effectiveness and safety of basal supported oral therapy with insulin glargine, in Japanese insulin-naive, type 2 diabetes patients, with or without microvascular complications: subanalysis of the observational, non-interventional, 24-week follow-up Add-on Lantus® to Oral Hypoglycemic Agents (ALOHA) study

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ABSTRACT

Aims: The aim of this study is to evaluate effectiveness and safety of basal supported oral therapy (BOT) using insulin glargine in insulin-naive Japanese patients, with and without microvascular complications.
Methods: This sub-group analysis of observational, non-interventional ALOHA study, assessed changes in glycemic parameters and glargine dose, at 24 weeks or at glargine discontinuation. Count of hypoglycemic episodes was based on physicians' documentation of patient reports. Patients were stratified according to presence/absence of microvascular complications, at baseline. Relationships between baseline patient characteristics and achievement of HbA1c <7% were examined by multivariate regression analysis.
Results: A total of 3631 patients, included during 2007–2009, were stratified in sub-groups: no complications ($n = 1889$), retinopathy ($n = 318$), neuropathy ($n = 297$), nephropathy ($n = 356$), retinopathy + neuropathy ($n = 174$), retinopathy + nephropathy ($n = 154$), neuropathy + nephropathy ($n = 142$), and retinopathy + neuropathy + nephropathy ($n = 301$). Changes in HbA1c, fasting and postprandial plasma glucose, and glargine daily dose were similar among patients with and without complications. Response-rate for achieving HbA1c <7.0% was highest in patients without complications (19.1%). In multivariate analysis, patients without complications showed significantly higher odds of attaining HbA1c <7%, independent of diabetes duration and baseline HbA1c levels. Patients with retinopathy + nephropathy had the lowest response-rate (8.8%) and highest hypoglycemic-rate (3.2%).
Conclusion: Japanese insulin-naive patients without complications, on BOT with glargine, show higher chances of attaining HbA1c <7.0% than those with complications.

1. Background

Diabetes poses a significant economic burden in Japan; an estimated 7.1 million adults in Japan had diabetes in 2010, which corresponds to 5.0% prevalence after adjusting to the world adult population (Shaw, Sicree, & Zimmet, 2010). Chronic hyperglycemia leads to microvascular complications such as nephropathy, retinopathy, and neuropathy; further decreasing quality of life, reducing life expectancy, and increasing the economic burden (Gerich, 2005; Girach, Manner, & Porta, 2006). In Japanese patients with type 2 diabetes mellitus (T2DM), medical costs of patients with nephropathy are 2.1-fold higher, retinopathy are 2.6-fold higher, and neuropathy are 3.3-fold higher than those without complications (Neville et al., 2009).

Earlier observational studies show that increased glycosylated hemoglobin (HbA1c) is associated with increase in risk of microvascular complications; and intensive glycemic control (as reflected by HbA1c) curbs the onset of microvascular complications of diabetes, slows their progression, and improves quality of life (Holman, Paul, Bethel, Matthews, & Neil, 2008; Sabanayagam et al., 2009; Selvin et al., 2011; Stratton et al., 2000; UK Prospective Diabetes Study (UKPDS) Group, 1998). However, randomized clinical trials show that benefit:risk ratio of intensive glucose lowering treatment in preventing microvascular complications is uncertain (Boussageon et al., 2011; Duckworth et al., 2009).

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Although the international guidelines recommend intensive glycemic control by early initiation and intensification of antidiabetic therapy with oral antidiabetic drugs (OADs) and/or insulin, along with lifestyle modification (Nathan et al., 2009; Rodbard et al., 2009), an earlier observational study in Asian patients highlights that in the real-world insulin initiation is delayed by approximately 9 years (Tsai et al., 2011). This can be attributed to physicians' and patients' reluctance to initiate insulin therapy (Marrero, 2007; Peyrot et al., 2005). The Diabetes Attitudes, Wishes and Needs (DAWN) Japan study also reports practical burdens as physicians' barriers to insulin initiation (Ishii, Iwamoto, & Tajima, 2012).

An earlier study in Japanese patients shows that 83.4% of patients have microvascular complications at the time of initiating insulin treatment (Freemantle et al., 2012; Kawamori et al., 2011). Studies in Western population postulate that in patients with existing microvascular complications and inadequate glycemic control, it is difficult to achieve strict glycemic control due to the risk of worsening the complications or cardiovascular events (Calles-Escandon et al., 2010; Patel et al., 2008; The Diabetes Control & Complications Trial Research Group, 1998). In a clinical trial setting, an earlier study in Japanese patients with T2DM, shows that intensive glycemic control by multiple insulin therapy delays onset and progression of diabetic complications (Ohkubo et al., 1995; Shichiri, Kishikawa, Ohkubo, & Wake, 2000). To substantiate the growing evidence in support of early insulin initiation before onset of microvascular complications to increase the chances of achieving glycemic targets, we conducted a sub-analysis of the Add-on Lantus® to Oral Hypoglycemic Agents (ALOHA) study (Ohtani & Ito, 2011). We evaluated effectiveness and safety of basal supported oral therapy (BOT) using insulin glargine in insulin-naive Japanese T2DM patients with and without microvascular complications.

2. Methods

2.1. Study design

ALOHA was an observational, non-interventional, post-marketing surveillance study that recruited 5223 patients having inadequately controlled T2DM, from 987 centers across Japan, between 2007 and 2009. The detailed design and methodology of the ALOHA study are published in earlier articles (Kadowaki, Ohtani, & Odawara, 2013; Odawara, Ohtani, & Kadowaki, 2012; Ohtani & Ito, 2011). This was a sub-analysis of the ALOHA cohort, in which we selected data of insulin-naive inadequately controlled T2DM patients, who were given BOT using insulin glargine, and were followed for 24 weeks to determine association of presence/absence of diabetic microvascular complications with the effectiveness and safety of BOT using insulin glargine.

This study was endorsed by the Health Authority in Japan and was conducted in accordance with the Good Post-marketing Study Practice (GPSP) (Kumano, 2012), and Good Vigilance Practice (GVP) (Good Pharmacovigilance Practices, 2014) in Japan.

2.2. Patients

The study included insulin-naive patients who satisfied the following criteria within 4 weeks of screening period before initiation of insulin glargine: (1) received treatment with OADs for ≥12 weeks, (2) had HbA1c (National Glycohemoglobin Standardization Program [NGSP][1]) values ≥7.9 and <12.5%, and (3) had body mass index (BMI) <30 kg/m^2. Insulin-naive patients with non-diabetic renal disorders were excluded.

[1] The NGSP values were selected based on the Japan Diabetic Society (JDS) values (≥7.5 and <12.0%, respectively). HbA1c data were collected as JDS values and then converted to NGSP values by the following conversion formula: HbA1c (NGSP) = 1.02 × HbA1c (JDS) + 0.25% with rounding off to the first decimal place (The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus et al., 2010).

2.3. Treatment

Initiation of insulin treatment and adjusting insulin doses were determined by attending physicians. Concomitant OADs were also selected by the physicians, as part of routine clinical care.

Patients who required additional insulin, for example, bolus insulin, were terminated to follow-up due to no longer fulfilling the inclusion criteria, which included patients treated with BOT using insulin glargine.

2.4. Data collection

All eligible patients' data were collected via paper-based case report forms. Data collected included background characteristics (gender, age, weight, duration of diabetes, disease history, complications, prior OADs, etc.), treatment details, and adverse events (AEs).

2.5. Study assessment

Safety and effectiveness data were collected over 24 weeks. Effectiveness parameters included HbA1c, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and weight. Safety was determined by documenting all AEs including hypoglycemia. In case of serious AEs, we evaluated seriousness, intervention, outcome, and causal relationship to insulin glargine.

Hypoglycemic episodes were counted by physicians' documentation (any hypoglycemic episodes and any symptoms derived from hypoglycemia), based on patients' reports. Hypoglycemia was defined as hypoglycemia-related symptoms as the adverse drug reaction or hypoglycemic episodes documented by physicians as the adverse drug reaction. Severe hypoglycemia included hypoglycemic episodes satisfying any of the following serious AEs criteria; (1) resulted in death, (2) life-threatening, (3) required or prolonged inpatient hospitalization, (4) persistently or significantly disabling/incapacitating, (5) a congenital anomaly, and/or (6) medically important.

We stratified total patients into two groups depending on the presence of diabetic microvascular complications: patients without complications and patients with complications. Patients with complications were further divided into sub-groups as follows: (1) retinopathy only, (2) neuropathy only, (3) nephropathy only, (4) retinopathy + neuropathy, (5) retinopathy + nephropathy, (6) neuropathy + nephropathy, and (7) retinopathy + neuropathy + nephropathy.

2.6. Statistical analyses

The baseline characteristic difference in the mean among diabetic microvascular complications groups was analyzed using one-way analysis of variance (ANOVA), and chi-square test was used for categorical variables. Changes in insulin glargine dose, HbA1c, FPG, PPG, and weight between baseline and endpoint were examined by paired t-test, according to diabetic microvascular complications groups. Symptomatic and severe hypoglycemia were examined by Fisher exact test. Multivariate logistic regression model was used to calculate odds ratios and 95% confidence intervals of diabetic microvascular complications adjusted for other factors predicting response to HbA1c <7.0% at endpoint. All statistical tests were two-sided at $\alpha = 0.05$. All statistical calculations were performed using IBM SPSS Statistics, version 21 (SPSS Inc., Chicago, IL), except Fisher exact test was executed by R version 2.15.2.

3. Results

3.1. Patient disposition and baseline characteristics

Of 5223 patients enrolled in the study, 5181 patients completed case report forms. Of these, 4219 patients were included in the safety analysis set (Supplementary file: Fig. 1). Of 3732 insulin-naive patients, we

Table 1
Baseline characteristics in total and sub-group patients by diabetic microvascular complications.

Characteristics		No complications	Retino	Neuro	Nephro	Retino + neuro	Retino + nephro	Neuro + nephro	Retino + neuro + nephro	Total	*P*
N		1889 (52.0)	318 (8.8)	297 (8.2)	356 (9.8)	174 (4.8)	154 (4.2)	142 (3.9)	301 (8.3)	3631	
Gender	Male, *n* (%)	1089 (57.6)	180 (56.6)	174 (58.6)	253 (71.1)	102 (59.0)	94 (61.0)	91 (64.1)	189 (62.8)	2172 (59.8)	<0.001[a]
	Female, *n* (%)	800 (42.4)	138 (43.4)	123 (41.4)	103 (28.9)	71 (41.0)	60 (39.0)	51 (35.9)	112 (37.2)	1458 (40.2)	
Age (years)	*n*	1887	317	296	354	174	154	142	299	3623	<0.001[b]
	Mean ± SD	61.1 ± 12.6	62.4 ± 10.6	64.1 ± 10.6	63.3 ± 11.8	64.9 ± 10.3	62.9 ± 10.7	66.9 ± 11.8	65.5 ± 11.3	62.5 ± 12.0	
Weight (kg)	*n*	1889	318	297	356	174	154	142	301	3631	0.009[b]
	Mean ± SD	62.0 ± 11.8	60.9 ± 11.2	61.3 ± 12.1	63.9 ± 11.9	60.6 ± 10.1	60.7 ± 10.9	60.7 ± 12.1	61.8 ± 11.5	61.8 ± 11.6	
BMI (kg/m^2)	*n*	1889	318	297	356	174	154	142	301	3631	0.008[b]
	Mean ± SD	23.8 ± 3.3	23.4 ± 3.1	23.5 ± 3.2	24.3 ± 3.4	23.4 ± 3.0	23.6 ± 3.4	23.5 ± 3.2	23.8 ± 3.3	23.7 ± 3.3	
HbA1c, (%)	*n*	1889	318	297	356	174	154	142	301	3631	0.020[b]
	Mean ± SD	9.47 ± 1.19	9.56 ± 1.15	9.64 ± 1.17	9.54 ± 1.15	9.55 ± 1.07	9.62 ± 1.22	9.70 ± 1.23	9.69 ± 1.23	9.54 ± 1.19	
Duration of diabetes, (years), *n* (%)	Missing data	137 (7.3)	11 (3.5)	15 (5.1)	16 (4.5)	5 (2.9)	8 (5.2)	4 (2.8)	17 (5.6)	213 (5.9)	<0.001[a]
	<1	36 (1.9)	3 (0.9)	3 (1.0)	1 (0.3)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	45 (1.2)	
	≥1, <5	296 (15.7)	24 (7.5)	32 (10.8)	32 (9.0)	7 (4.0)	14 (9.1)	7 (4.9)	14 (4.7)	426 (11.7)	
	≥5	1420 (75.2)	280 (88.1)	247 (83.2)	307 (86.2)	160 (92.0)	132 (85.7)	131 (92.3)	270 (89.7)	2947 (81.2)	
Patients with pre-study OADs, *n* (%)	<3	1215 (64.3)	168 (52.8)	185 (62.3)	203 (57.0)	97 (55.7)	87 (56.5)	87 (61.3)	182 (60.5)	2224 (61.3)	0.001[a]
	≥3	674 (35.7)	150 (47.2)	112 (37.7)	153 (43.0)	77 (44.3)	67 (43.5)	55 (38.7)	119 (39.5)	1407 (38.7)	
eGFR (mL/min/1.73 m^2), *n* (%)	Missing data	497 (26.3)	76 (23.9)	64 (21.5)	76 (21.3)	38 (21.8)	26 (16.9)	31 (21.8)	63 (20.9)	871 (24.0)	<0.001[a]
	≥90	508 (26.9)	82 (25.8)	76 (25.6)	88 (24.7)	46 (26.4)	41 (26.6)	30 (21.1)	48 (15.9)	919 (25.3)	
	≥60, <90	703 (37.2)	137 (43.1)	131 (44.1)	110 (30.9)	74 (42.5)	54 (35.1)	51 (35.9)	100 (33.2)	1360 (37.5)	
	<60	181 (9.6)	23 (7.2)	26 (8.8)	82 (23.0)	16 (9.2)	33 (21.4)	30 (21.1)	90 (29.9)	481 (13.2)	

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; Nephro, nephropathy; Neuro, neuropathy; OADs, oral antidiabetic drugs; Retino, retinopathy; SD, standard deviation.
[a] Chi square test.
[b] Analysis of variance test.

excluded 101 patients with non-diabetic renal disorders, and analyzed 3631 insulin-naive patients. The analyzed patients were divided as patients without microvascular complications (52.0%, $n = 1889$) and patients with microvascular complications (48.0%, $n = 1742$). The latter group was further divided into seven sub-groups as per the various combinations of diabetic microvascular complications.

Baseline characteristics of total and sub-group patients are presented in Table 1. A total of 59.8% of patients were male, with mean age 62.5 ± 12.0 years, and mean body mass index 23.7 ± 3.3 kg/m^2. Majority of patients (81.2%) had duration of T2DM ≥5 years, with mean HbA1c 9.54% ± 1.19%. There were 13.2% of patients with estimated glomerular filtration rate (eGFR) levels <60 mL/min/1.73 m^2, indicating poor renal function. There were 9.6% of patients without complications with eGFR <60 mL/min/1.73 m^2. Statistical analysis was carried out to find the difference between measured variables of different groups. The result of ANOVA showed that the difference in mean weight, BMI and HbA1c among the groups were statistically significant.

Before the study, 61.3% of patients received <3 OADs. The most common OADs administered before the trial were sulfonylureas ($n = 3587$, 85.0%), biguanides ($n = 1991$, 47.2%) and alpha glucosidase inhibitors ($n = 1971$, 46.7%) and during the trial were sulfonylureas ($n = 3558$, 84.3%), biguanides ($n = 1990$, 47.2%) and alpha-glucosidase inhibitors ($n = 2030$, 48.1%). In 87% ($n = 3171$) patients there was no change in OADs before and during the study. (Table 2) Further details on the type of OADs have been published earlier (Ohtani & Ito, 2011).

A total of 3182 (87.6%) patients completed the study, while 449 (12.4%) patients discontinued in <24 weeks. The mean starting dose, endpoint dose and change of insulin dose in patients without complications were 6.1, 9.5 and +3.4 U/day, respectively. Among the sub-groups, the highest increase in the insulin dose was observed in the nephropathy alone (starting: 5.8 U/day, endpoint: 9.9 U/day, change: +4.1 U/day) and retinopathy + nephropathy groups (starting: 5.6 U/day, endpoint: 9.7 U/day, change: +4.1 U/day), followed by retinopathy + neuropathy + nephropathy group (starting: 5.5 U/day, endpoint: 9.5 U/day, change: +4.0 U/day) (Table 2).

Table 3 presents data on change in HbA1c, FPG, PPG, and responder rate among total and sub-group patients based on diabetic microvascular complications. Among patients, without complications, the HbA1c decreased by 1.47%, along with decrease in FPG (62.3 mg/mL) and PPG (67.3 mg/mL). Among patients with complications, patients with neuropathy + nephropathy showed highest decrease in HbA1c (1.59%), followed by patients with neuropathy (1.52%). Patients with neuropathy + nephropathy showed highest decrease in FPG (86.5 mg/mL), followed by patients with nephropathy (71.1 mg/mL). In case of decrease in PPG, patients with neuropathy + nephropathy showed highest decrease in PPG (84.3 mg/mL), followed by patients with retinopathy + nephropathy (80.1 mg/mL).

Among all sub-groups, there was a statistically significant difference in responder rates of HbA1c <7.0% at endpoint. Response rate of achieving HbA1c <7.0% was the highest in patients without any diabetic microvascular complications (19.1%). Patients with retinopathy + nephropathy had the lowest response rate (8.8%).

The weight change in patients without complications during the study period was 0.8 kg. Incidence of documented symptomatic hypoglycemia by diabetic microvascular complications was marginally statistically significant across the patient sub-groups. Patients with retinopathy + -nephropathy had the highest hypoglycemic rate (3.2%), whereas patients with neuropathy + nephropathy had no hypoglycemic event. Among patients without complications, 1.0 and 0.1% of patients had hypoglycemia and severe hypoglycemia, respectively (Table 4).

3.2. Association between patient characteristics and achieving HbA1c <7% in insulin-naive patients: multivariate analysis

Table 5 shows the relationships between baseline patient characteristics and likelihood of reaching HbA1c <7%, as tested by

Table 2
Change in insulin glargine dose and proportion of patients with change in OADs by diabetic microvascular complications.

Characteristics		No complications	Retino	Neuro	Nephro	Retino + neuro	Retino + nephro	Neuro + nephro	Retino + neuro + nephro	Total	*P*
Insulin dose, U/day											
Starting	*n*	1888	318	296	354	173	154	140	300	3623	<0.001[a]
	mean ± SD	6.1 ± 3.7	5.6 ± 3.1	6.3 ± 3.7	5.8 ± 2.4	5.9 ± 2.7	5.6 ± 2.4	5.7 ± 2.8	5.5 ± 2.5	6.0 ± 3.3	
Endpoint	*n*	1888	318	296	354	173	154	140	300	3623	
	mean ± SD	9.5 ± 5.5	8.9 ± 4.6	9.5 ± 5.4	9.9 ± 5.5	9.2 ± 4.8	9.7 ± 5.8	9.6 ± 5.9	9.5 ± 5.1	9.5 ± 5.4	
Change	*n*	1888	318	296	354	173	154	140	300	3623	
	mean ± SD	3.4 ± 4.7	3.3 ± 4.1	3.2 ± 4.6	4.1 ± 5.2	3.3 ± 4.2	4.1 ± 5.8	3.8 ± 5.6	4.0 ± 4.8	3.5 ± 4.8	
Insulin dose per weight, U/kg/day											
Starting	*n*	1888	318	296	354	173	154	140	300	3623	<0.001[a]
	mean ± SD	0.102 ± 0.060	0.096 ± 0.057	0.105 ± 0.064	0.093 ± 0.044	0.099 ± 0.044	0.096 ± 0.047	0.096 ± 0.045	0.092 ± 0.046	0.099 ± 0.056	
Endpoint	*n*	1332	249	227	262	126	119	112	231	2658	
	mean ± SD	0.154 ± 0.084	0.147 ± 0.075	0.156 ± 0.084	0.156 ± 0.081	0.151 ± 0.075	0.166 ± 0.098	0.159 ± 0.098	0.154 ± 0.086	0.154 ± 0.084	
Change	*n*	1332	249	227	262	126	119	112	231	2658	
	mean ± SD	0.055 ± 0.075	0.053 ± 0.064	0.052 ± 0.070	0.063 ± 0.077	0.053 ± 0.070	0.071 ± 0.094	0.063 ± 0.093	0.061 ± 0.077	0.057 ± 0.76	
Proportion of patients with change in OADs before and during the study											
Change in OADs	*n* (%)	226 (12.0)	46 (14.5)	43 (14.5)	42 (11.8)	20 (11.5)	23 (14.9)	22 (15.5)	38 (12.6)	460 (12.7)	0.678[b]
No change in OADs	*n* (%)	1663 (88.0)	272 (85.5)	254 (85.5)	314 (88.2)	154 (88.5)	131 (85.1)	120 (84.5)	263 (87.4)	3171 (87.3)	

Abbreviations: Nephro, nephropathy; Neuro, neuropathy; Retino, retinopathy; SD, standard deviation.
[a] Paired *t* test.
[b] Chi square test.

multivariate logistic regression analysis in total 3239 patients after excluding patients with missing values ($n = 392$). Higher baseline HbA1c (OR 0.69, 95% CI: 0.63, 0.76), and presence of diabetic retinopathy (OR 0.60, 95% CI: 0.41, 0.88), neuropathy (OR 0.67, 95% CI: 0.46, 0.99), retinopathy + nephropathy (OR 0.44, 95% CI: 0.24, 0.81), retinopathy + neuropathy + nephropathy (OR 0.65, 95% CI: 0.44, 0.96) decreased the odds of achieving target HbA1c. Findings of this analysis showed that duration of diabetes <1 year (OR 3.05, 95% CI: 1.48, 6.31) and patients with older age (OR 1.02, 95% CI: 1.01, 1.03) increased chances of achieving HbA1c <7%. Thus, patients without complications showed significantly higher odds of attaining HbA1c <7% than patients with complications, independently of duration of diabetes and baseline HbA1c levels.

4. Discussion

This sub-analysis of the observational, non-interventional, 24-week post-marketing surveillance ALOHA study in Japan provides, for the first time, detailed real-life information on effectiveness and safety of BOT using insulin glargine in insulin-naive T2DM patients according to presence/absence of diabetic microvascular complications.

T2DM is a progressive disease characterized by gradual loss of insulin secretion, and the risk of developing microvascular complications increases with diabetes duration and the severity of hyperglycemia (Fowler, 2008). Diabetic retinopathy is known to cause blindness among adults aged 20–74 years. In diabetic neuropathy, asymptomatic distal symmetric polyneuropathy might pose risk for insensate injury to feet, while autonomic neuropathy might lead to morbidity and even mortality. Diabetic nephropathy is also known to be the leading cause of end stage renal disease (American Diabetes Association, 2013). Considering various modifiable risk factors of microvascular complications, such as hyperglycemia, duration of diabetes, hypertension, metabolic syndrome, etc. (Abdul-Ghani et al., 2006; Paisey et al., 1984; Ramachandran et al., 1999), and associations among the complications (Girach et al., 2006), it is crucial to prevent microvascular disease, to reduce the associated morbidity and mortality. Increasing awareness and patient/physician education regarding early diagnosis/screening for T2DM and early insulin initiation might help in controlling microvascular complications and related health and economic burden (Marrero, 2007; Peyrot et al., 2005; Spijkerman et al., 2003).

An earlier study in Japanese patients shows that 83.4% of T2DM patients have microvascular complications at the time of initiating insulin treatment (Freemantle et al., 2012; Kawamori et al., 2011). In the present study also, as many as 48% of the insulin-naive patients had various combinations of microvascular complications, including retinopathy, neuropathy, and nephropathy. Early initiation of basal insulin in inadequately controlled T2DM patients demonstrates improvement in glycemic control (Blickle et al., 2009; Nathan et al., 2009), which in turn decreases risk of microvascular complications (UK Prospective Diabetes Study (UKPDS) Group, 1998; Holman et al., 2008; Ohkubo et al., 1995; Shichiri et al., 2000). Insulin glargine is convenient, efficacious and safe in the treatment of T2DM (Barnett, 2006). An earlier clinical trial in Japanese T2DM patients, demonstrates that BOT with insulin glargine decreases HbA1c levels during 28-week study period, suggesting suppression of progression of complications (Kawamori, Iwamoto, Kadowaki, & Iwasaki, 2003). In another study in Japanese T2DM insulin-naive patients, BOT using insulin glargine significantly improved HbA1c levels, without causing serious hypoglycemia (Suzuki et al., 2012). In the present study also, initiation of insulin glargine in BOT showed reductions in HbA1c, FPG and PPG, along with low rate of hypoglycemia. The present study also demonstrated that more patients without microvascular complications achieve HbA1c <7% as compared to patients with complications.

In the present study, multivariate logistic regression analysis revealed that as compared to the patients without any diabetic

Table 3
Change in HbA1c, FPG, PPG, and responder rate by diabetic microvascular complications.

Characteristics		No complications	Retino	Neuro	Nephro	Retino + neuro	Retino + nephro	Neuro + nephro	Retino + neuro + nephro	Total	*P*
HbA1c (%), mean ± SD	*n*	1889	318	297	356	174	154	142	301	3631	<0.001[a]
	Starting	9.47 ± 1.19	9.56 ± 1.15	9.64 ± 1.17	9.54 ± 1.15	9.55 ± 1.07	9.62 ± 1.22	9.70 ± 1.23	9.69 ± 1.23	9.54 ± 1.19	
	n	1680	291	263	324	154	136	130	266	3244	
	Endpoint	8.00 ± 1.23	8.15 ± 1.20	8.15 ± 1.13	8.12 ± 1.15	8.16 ± 1.09	8.23 ± 1.20	8.08 ± 1.22	8.25 ± 1.27	8.08 ± 1.21	
	n	1680	291	263	324	154	136	130	266	3244	
	Change	−1.47 ± 1.30	−1.40 ± 1.20	−1.52 ± 1.19	−1.42 ± 1.27	−1.38 ± 1.11	−1.38 ± 1.31	−1.59 ± 1.24	−1.45 ± 1.36	−1.46 ± 1.28	
FPG (mg/mL),mean ± SD	*n*	429	60	45	53	31	25	31	55	729	<0.001[a]
	Starting	198.4 ± 62.3	197.4 ± 57.9	206.1 ± 58.3	209.0 ± 57.1	197.5 ± 59.1	204.7 ± 58.7	218.9 ± 91.6	199.1 ± 63.6	200.7 ± 62.6	
	n	429	60	45	53	31	25	31	55	729	
	Endpoint	136.1 ± 42.4	149.7 ± 51.6	141.9 ± 50.5	138.0 ± 40.0	130.5 ± 30.7	141.4 ± 34.6	132.5 ± 40.0	144.1 ± 48.1	138.1 ± 43.3	
	n	429	60	45	53	31	25	31	55	729	
	Change	−62.3 ± 63.9	−47.7 ± 62.6	−64.2 ± 56.5	−71.1 ± 65.2	−67.0 ± 58.8	−63.3 ± 52.2	−86.5 ± 81.4	−55.0 ± 65.7	−62.6 ± 64.0	
PPG (mg/mL),mean ± SD	*n*	454	74	86	84	45	39	35	77	894	<0.001[a]
	Starting	264.1 ± 85.6	261.2 ± 85.8	290.4 ± 75.9	260.4 ± 88.8	266.0 ± 83.7	259.9 ± 83.7	302.0 ± 79.4	276.4 ± 79.8	268.5 ± 84.5	
	n	454	74	86	84	45	39	35	77	894	
	Endpoint	196.7 ± 71.9	190.4 ± 57.9	219.0 ± 65.6	203.3 ± 70.4	195.4 ± 62.6	179.9 ± 75.0	217.7 ± 60.7	221.8 ± 77.4	201.1 ± 70.5	
	n	454	74	86	84	45	39	35	77	894	
	Change	−67.3 ± 91.8	−70.8 ± 89.2	−71.4 ± 86.1	−57.2 ± 92.1	−70.6 ± 91.0	−80.1 ± 94.8	−84.3 ± 90.0	−54.6 ± 86.3	−67.3 ± 90.5	
HbA1c <7%	*N*	1680	291	263	324	154	136	130	266	3244	<0.001[b]
	n (%)	321 (19.1)	34 (11.7)	34 (12.9)	51 (15.7)	19 (12.3)	12 (8.8)	17 (13.1)	35 (13.2)	523 (16.1)	

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; Nephro, nephropathy; Neuro, neuropathy; PPG, postprandial glucose; Retino, retinopathy; SD, standard deviation.
[a] Paired t test.
[b] Chi square test.

microvascular complications, patients with complications (especially retinopathy, alone or in combination with neuropathy or nephropathy) showed significantly lower odds of attaining glycemic control of HbA1c <7%. The statistical model of multivariate regression analysis, eliminated the effect of confounding factors, showing that the diabetic microvascular complications were risk factors of attaining the good glycemic control measured by HbA1c (<7%), independent of duration of diabetes and baseline HbA1c levels. These results are in line with the earlier observational registry, International Diabetes Management Practice Study (IDMPS), which showed that in Asian T2DM patients, lack of microvascular complications is predictor of HbA1c <7% (OR 0.82, 95% CI 0.693, 0.979) (Chan et al., 2009).

The benefits of achieving adequate glycemic control with respect to delaying onset and progression of diabetic microvascular complications, are counter-balanced with the relative risk of severe hypoglycemia by 30% (Hemmingsen et al., 2011; Ismail-Beigi et al., 2010). In Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) study, severe hypoglycemia is associated with major microvascular events (hazards ratio, 1.81; 95% CI 1.19, 2.74) (Zoungas et al., 2010). Diabetic complications such as peripheral neuropathy, renal insufficiency, and coronary artery disease are independent risk factors for first and multiple events of severe hypoglycemia (Davis et al., 2010; Lin et al., 2010). In line with the earlier evidence, in the current study also, hypoglycemia was associated with presence of diabetic complication (s) (relative risk 1.36, 95% CI: 0.66, 2.83) (Odawara, Kadowaki, & Naito, 2014). In the present study, though there was some difference in incidence of hypoglycemia among diabetic microvascular complications, the difference and the absolute risk itself were small.

The present sub-analysis of the observational ALOHA study provides information on effectiveness and safety of BOT using insulin glargine as per the presence/absence of microvascular complications, in real-life clinical practice in insulin-naive T2DM patients in Japan having inadequate glycemic control. The stratification on the basis of type of complications lays the foundation for future exploratory research to devise newer strategies for the attainment of glycemic targets in patients with specific complications.

However, this population might not represent general T2DM patient population who initiate insulin glargine. In addition, this sub-analysis does not provide information on the worsening of the microvascular complications from baseline to the end of the study, after initiating BOT using insulin glargine. Unlike a treat-to-target trial, the present observational study has no interventional target of glycemic control. In this study, we gathered data from the clinical records as reported by physicians, without any other validation. Hence, because of the observational nature of the study, it is likely that prevalence of diabetic microvascular complications is underestimated or misclassified, due to the lack of precise definitions of the complications. The changes in HbA1c in the various groups with and without complications though statistically significant, need to be tested in various clinical settings in order to ascertain that they are clinically meaningful.

In conclusion, in Japanese insulin-naive patients with T2DM treated with BOT using insulin glargine, patients without any complications show higher chances of reaching glycemic control than those with complications, independent of duration of diabetes and baseline HbA1c levels. Increasing awareness and patient/physician education regarding early diagnosis of T2DM and early insulin initiation might help in controlling microvascular complications and related health and economic burden.

Authors' contributions

Sanofi K.K. was responsible for the study design, study conduct and statistical analysis. YN was responsible for the statistical analysis. MO and TK made significant suggestion to the analysis and interpretation

Table 4
Change in weight and incidence of hypoglycemia by diabetic microvascular complications.

Characteristics		No complications	Retino	Neuro	Nephro	Retino + neuro	Retino + nephro	Neuro + nephro	Retino + neuro + nephro	Total	*P*
Weight, kg (mean ± SD)	*n*	1333	249	227	262	127	119	113	232	2662	<0.001[a]
	Starting	62.5 ± 11.8	61.4 ± 11.4	61.6 ± 12.2	64.5 ± 11.5	60.1 ± 9.0	61.1 ± 10.7	61.3 ± 11.8	61.7 ± 11.6	62.2 ± 11.6	
	n	1333	249	227	262	127	119	113	232	2662	
	Endpoint	63.3 ± 11.9	62.3 ± 11.4	62.9 ± 12.4	65.7 ± 11.8	60.9 ± 8.8	62.2 ± 11.2	62.1 ± 12.3	62.5 ± 11.3	63.1 ± 11.7	
	n	1333	249	227	262	127	119	113	232	2662	
	Change	0.8 ± 2.5	0.9 ± 2.5	1.3 ± 2.3	1.2 ± 2.5	0.9 ± 2.2	1.1 ± 2.7	0.8 ± 2.8	0.8 ± 2.7	0.9 ± 2.5	0.050[b]
Hypoglycemia	*n*	1889	318	297	356	174	154	142	301	3631	
	n (%)	18 (1.0)	1 (0.3)	6 (2.0)	2 (0.6)	1 (0.6)	5 (3.2)	0 (0.0)	5 (1.7)	38 (1.0)	
Severe hypoglycemia	*N*	1889	318	297	356	174	154	142	301	3631	0.375[b]
	n (%)	2 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	4 (0.1)	

Abbreviations: Nephro, nephropathy; Neuro, neuropathy; Retino, retinopathy; SD, standard deviation.
[a] Paired t test.
[b] Fisher exact test.

Table 5
Association of patient characteristics with achievement of HbA1c < 7% in insulin-naive T2DM patients ($n = 3239$).

Patient characteristics	Categories	OR	95% CI		*P* value
			Lower	Upper	
Sex	Men	1.18	0.97	1.44	0.098
	Women	Reference			
Age	1 year increment	1.02	1.01	1.03	<0.001
Baseline HbA1c	1% increment	0.69	0.63	0.76	<0.001
Duration of diabetes	<1 year	3.05	1.48	6.31	0.003
	≥1 year, <5 years	1.25	0.93	1.69	0.135
	≥5 years	Reference			
	Unknown	1.67	1.16	2.41	0.006
Diabetic microvascular complications	None	Reference			
	Retino	0.60	0.41	0.88	0.008
	Neuro	0.67	0.46	0.99	0.044
	Nephro	0.79	0.56	1.10	0.158
	Retino + neuro	0.61	0.37	1.01	0.056
	Retino + nephro	0.44	0.24	0.81	0.008
	Neuro + nephro	0.64	0.38	1.10	0.105
	Retino + neuro + nephro	0.65	0.44	0.96	0.029

Abbreviations: CI, confidence interval; HbA1c, glycosylated hemoglobin; Nephro, nephropathy; Neuro, neuropathy; OR, odds ratio; Retino, retinopathy.

of data. YN drafted the manuscript, MO and TK reviewed and revised the draft manuscript. All authors have reviewed and approved the final version of this manuscript.

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References

Abdul-Ghani, M., Nawaf, G., Nawaf, F., Itzhak, B., Minuchin, O., Vardi, P., et al. (2006). Increased prevalence of microvascular complications in type 2 diabetes patients with the metabolic syndrome. *The Israel Medical Association Journal*, *8*, 378–382.

American Diabetes Association (2013). Standards of medical care in diabetes—2013. *Diabetes Care*, *36*(Suppl. 1), S11–S66.

Barnett, A. H. (2006). Insulin glargine in the treatment of type 1 and type 2 diabetes. *Vascular Health and Risk Management*, *2*, 59–67.

Blickle, J. F., Hancu, N., Piletic, M., Profozic, V., Shestakova, M., Dain, M. P., et al. (2009). Insulin glargine provides greater improvements in glycaemic control vs. intensifying lifestyle management for people with type 2 diabetes treated with OADs and 7–8% A1c levels. The TULIP study. *Diabetes, Obesity & Metabolism*, *11*, 379–386.

Boussageon, R., Bejan-Angoulvant, T., Saadatian-Elahi, M., Lafont, S., Bergeonneau, C., Kassai, B., et al. (2011). Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. *BMJ*, *343*, d4169.

Calles-Escandon, J., Lovato, L. C., Simons-Morton, D. G., Kendall, D. M., Pop-Busui, R., Cohen, R. M., et al. (2010). Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care*, *33*, 721–727.

Chan, J. C., Gagliardino, J. J., Baik, S. H., Chantelot, J. M., Ferreira, S. R., Hancu, N., et al. (2009). Multifaceted determinants for achieving glycemic control: The International Diabetes Management Practice Study (IDMPS). *Diabetes Care*, *32*, 227–233.

Davis, T. M., Brown, S. G., Jacobs, I. G., Bulsara, M., Bruce, D. G., & Davis, W. J. (2010). Determinants of severe hypoglycemia complicating type 2 diabetes: The Fremantle Diabetes Study. *The Journal of Clinical Endocrinology and Metabolism*, *95*, 2240–2247.

Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P. D., et al. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. *The New England Journal of Medicine*, *360*, 129–139.

Fowler, M. (2008). Microvascular and macrovascular complications of diabetes. *Clinical Diabetes*, *26*, 77–82.

Freemantle, N., Balkau, B., Danchin, N., Wang, E., Marre, M., Vespasiani, G., et al. (2012). Factors influencing initial choice of insulin therapy in a large international non-interventional study of people with type 2 diabetes. *Diabetes, Obesity & Metabolism*, *14*, 901–909.

Gerich, J. E. (2005). The importance of tight glycemic control. *The American Journal of Medicine*, *118*, 7S–11S.

Girach, A., Manner, D., & Porta, M. (2006). Diabetic microvascular complications: Can patients at risk be identified? A review. *International Journal of Clinical Practice*, *60*, 1471–1483.

Good Pharmacovigilance Practices. European Medicines Agency. Available at. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp (Last Accessed Jul. 24, 2014)

Hemmingsen, B., Lund, S. S., Gluud, C., Vaag, A., Almdal, T., Hemmingsen, C., et al. (2011). Intensive glycaemic control for patients with type 2 diabetes: Systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*, *343*, d6898.

Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. (2008). 10-Year follow-up of intensive glucose control in type 2 diabetes. *The New England Journal of Medicine*, *359*, 1577–1589.

Ishii, H., Iwamoto, Y., & Tajima, N. (2012). An exploration of barriers to insulin initiation for physicians in Japan: Findings from the Diabetes Attitudes, Wishes and Needs (DAWN) JAPAN Study. *PLoS ONE*, *7*, e36361.

Ismail-Beigi, F., Craven, T., Banerji, M. A., Basile, J., Calles, J., Cohen, R. M., et al. (2010). Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: An analysis of the ACCORD randomised trial. *Lancet*, *376*, 419–430.

Kadowaki, T., Ohtani, T., & Odawara, M. (2013). Baseline predictive factors for glycemic control in Japanese type 2 diabetes patients treated with insulin glargine plus oral antidiabetic drugs: ALOHA study subanalysis. *Diabetology International*, *4*, 16–22.

Kawamori, R., Iwamoto, Y., Kadowaki, T., & Iwasaki, M. (2003). Efficacy and safety of insulin glargine in concurrent use with oral hypoglycemic agents for the treatment of type 2 diabetic patients. *Rinsho Iyaku*, *19*, 445–464.

Kawamori, R., Node, K., Hanafusa, T., Atsumi, Y., Naito, Y., Oka, Y., et al. (2011). Baseline and 1-year interim follow-up assessment of Japanese patients initiating insulin therapy enrolled in the CREDIT Study. *International Diabetes Federation 2011 World Diabetes Congress* (pp. P-1426).

Kumano, S. (2012). GPSP: Good post-marketing study practice. *Nihon Yakurigaku Zasshi*, *140*, 81–84.

Lin, Y. Y., Hsu, C. W., Sheu, W. H., Chu, S. J., Wu, C. P., & Tsai, S. H. (2010). Risk factors for recurrent hypoglycemia in hospitalized diabetic patients admitted for severe hypoglycemia. *Yonsei Medical Journal*, *51*, 367–374.

Marrero, D. G. (2007). Overcoming patient barriers to initiating insulin therapy in type 2 diabetes mellitus. *Clinical Cornerstone*, *8*, 33–43.

Nathan, D. M., Buse, J. B., Davidson, M. B., Ferrannini, E., Holman, R. R., Sherwin, R., et al. (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, *32*, 193–203.

Neville, S. E., Boye, K. S., Montgomery, W. S., Iwamoto, K., Okamura, M., Hayes, R. P., et al. (2009). Diabetes in Japan: A review of disease burden and approaches to treatment. *Diabetes/Metabolism Research and Reviews*, *25*, 705–716.

Odawara, M., Kadowaki, T., & Naito, Y. (2014). Incidence and predictors of hypoglycemia in Japanese patients with type 2 diabetes treated by insulin glargine and oral antidiabetic drugs in real-life: ALOHA post-marketing surveillance study sub-analysis. *Diabetology and Metabolic Syndrome*, *6*, 20.

Odawara, M., Ohtani, T., & Kadowaki, T. (2012). Dosing of insulin glargine to achieve the treatment target in Japanese type 2 diabetes on a basal supported oral therapy regimen in real life: ALOHA Study subanalysis. *Diabetes Technology & Therapeutics*, *14*, 635–643.

Ohkubo, Y., Kishikawa, H., Araki, E., Miyata, T., Isami, S., Motoyoshi, S., et al. (1995). Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. *Diabetes Research and Clinical Practice*, *28*, 103–117.

Ohtani, T., & Ito, T. (2011). Safety and effectiveness of BOT (basal supported oral therapy) using insulin glargine in Japanese patients with type 2 diabetes—results from postmarketing surveillance of insulin glargine (ALOHA study). *Shinyaku to Rinsho (Journal of New Remedies & Clinics)*, *60*, 458–475.

Paisey, R. B., Arredondo, G., Villalobos, A., Lozano, O., Guevara, L., Kelly, S., et al. (1984). Association of differing dietary, metabolic, and clinical risk factors with microvascular complications of diabetes: A prevalence study of 503 Mexican type II diabetic subjects. II. *Diabetes Care*, *7*, 428–433.

Patel, A., MacMahon, S., Chalmers, J., Neal, B., Billot, L., Woodward, M., et al. (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *The New England Journal of Medicine*, *358*, 2560–2572.

Peyrot, M., Rubin, R. R., Lauritzen, T., Skovlund, S. E., Snoek, F. J., Mathews, D. R., et al. (2005). Resistance to insulin therapy among patients and providers: Results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care*, *28*, 2673–2679.

Ramachandran, A., Snehalatha, C., Satyavani, K., Latha, E., Sasikala, R., Vijay, V., et al. (1999). Prevalence of vascular complications and their risk factors in type 2 diabetes. *The Journal of the Association of Physicians of India*, *47*, 1152–1156.

Rodbard, H. W., Jellinger, P. S., Davidson, J. A., Einhorn, D., Garber, A. J., Grunberger, G., et al. (2009). Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: An algorithm for glycemic control. *Endocrine Practice*, *15*, 540–559.

Sabanayagam, C., Liew, G., Tai, E. S., Shankar, A., Lim, S. C., Subramaniam, T., et al. (2009). Relationship between glycated haemoglobin and microvascular complications: Is there a natural cut-off point for the diagnosis of diabetes? *Diabetologia*, *52*, 1279–1289.

Selvin, E., Ning, Y., Steffes, M. W., Bash, L. D., Klein, R., Wong, T. Y., et al. (2011). Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. *Diabetes*, *60*, 298–305.

Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, *87*, 4–14.

Shichiri, M., Kishikawa, H., Ohkubo, Y., & Wake, N. (2000). Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*, *23*, B21–B29.

Spijkerman, A. M., Dekker, J. M., Nijpels, G., Adriaanse, M. C., Kostense, P. J., Ruwaard, D., et al. (2003). Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: The Hoorn Screening Study. *Diabetes Care*, *26*, 2604–2608.

Stratton, I. M., Adler, A. I., Neil, H. A., Matthews, D. R., Manley, S. E., Cull, C. A., et al. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ*, *321*, 405–412.

Suzuki, D., Umezono, T., Miyauchi, M., Kimura, M., Yamamoto, N., Tanaka, E., et al. (2012). Effectiveness of basal-supported oral therapy (BOT) using insulin glargine in patients with poorly controlled type 2 diabetes. *The Tokai Journal of Experimental and Clinical Medicine*, *37*, 41–46.

The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino, Y., Nanjo, K., Tajima, N., Kadowaki, T., Kashiwagi, A., Araki, E., et al. (2010). Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. *Journal of Diabetes Investigation*, *1*, 212–228.

The Diabetes Control and Complications Trial Research Group (1998). Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Archives of Ophthalmology*, *116*, 874–886.

Tsai, S. T., Pathan, F., Ji, L., Yeung, V. T., Chadha, M., Suastika, K., et al. (2011). First insulinization with basal insulin in patients with type 2 diabetes in a real-world setting in Asia. *Journal of Diabetes*, *3*, 208–216.

UK Prospective Diabetes Study (UKPDS) Group (1998). Intensive blood–glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, *352*, 837–853.

Zoungas, S., Patel, A., Chalmers, J., de Galan, B. E., Li, Q., Biostat, M., et al. (2010). Severe hypoglycemia and risks of vascular events and death. *The New England Journal of Medicine*, *363*, 1410–1418.